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HORMETIC INFLUENCE OF GLUCOCORTICOIDS ON HUMAN MEMORY

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□ *In this paper, we discuss the effects of glucocorticoids on human learning and memory using the recent model of hormesis proposed by Calabrese and collaborators. Although acute increases in glucocorticoids have been shown to impair memory function in humans, other studies report no such impairments or, in contrast, beneficial effects of acute glucocorticoid increases on human memory function. We summarize these studies and assess whether the wealth of data obtained in humans with regard to the effects of acute increase of glucocorticoids on human cognition are in line with a hormetic function. We then discuss several factors that will have to be taken into account in order to confirm the presence of a hormetic function between glucocorticoids and human cognitive performance.*

Keywords. Glucocorticoids, Noradrenergic Hormones, Hippocampus, Frontal, Memory, Receptors, Hormesis, Humans

INTRODUCTION

Stress is a popular topic these days. A week seldom passes without hearing or reading about stress and its deleterious effects on health and/or cognitive functions such as learning and memory. Given these negative consequences, many types of stress management therapies have emerged, which aim to decrease stress and ultimately, prevent its negative impact on learning and memory. The popular idea that stress impairs learning and mem-

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ory has been widely confirmed in the scientific literature. Indeed, about 40 years of research has shown that the negative effects of stress on learning and memory are due to the fact that stress hormones (particularly glucocorticoids), released during a stressful experience, easily cross the blood-brain barrier and impact brain structures known to be involved in learning and memory (for a complete review, see Lupien & Lepage, 2001).

There is a great paradox, however, in the field of stress research that relates to the fact that stress hormones are not consistently linked to impaired learning and memory. In various animal and human studies, stress hormones have been shown to increase the capacity to learn and/or consolidate new information (for a review, see DeKloet *et al.*, 1999 and Roozendaal, 2002). In fact, in both animals and humans, many studies reveal the presence of an inverted-U shape function between circulating stress hormone levels and memory performance (for a complete review, see Lupien & McEwen, 1997). Although the validity of the inverted-U shape function between glucocorticoids and memory is still called into question, it is of interest to note that the observed biphasic effects of glucocorticoids on memory may be part of a larger family of endogenous and exogenous substances showing a similar function, i.e. a function that has been termed "hormesis".

THE CONCEPT OF HORMESIS

The term hormesis refers to how a typically toxic substance can have beneficial effects at low doses (for a review, see Calabrese and Baldwin, 2003). Hormesis has recently been the subject of what has been called the "dose-response revolution" (Calabrese and Baldwin, 2003). This revolution came about with the changing perception that the nature of the dose-response observed in toxicology, biology, and radiation data is not linear or threshold, as originally postulated, but rather U-shaped. Using scientific data from over 3,000 sources from a variety of research fields, Calabrese and collaborators (Calabrese *et al.*, 1999; Calabrese and Baldwin, 2001, 2002, 2003; Calabrese, 2002) have shown that the function relating a substance to its effects follows an inverted-U shape. This finding could have a tremendous impact on social policies and scientific thinking since it would suggest, for example, that low doses of ionizing radiation, which were previously thought to be harmful (the linear dose effect model), may not be harmful after all or may even have net benefits (see Sagan, 1989).

A schematic representation of a hormetic function is depicted in Figure 1. Here, the general form of the U-shaped dose-response curve shows response relative to a reference level, which includes a region of apparent improvement as well as a region of toxic or adverse effects. In this Figure, the hormetic zone is defined as the entire zone of the function related to enhancing and impairing effects. What is important to note in the context

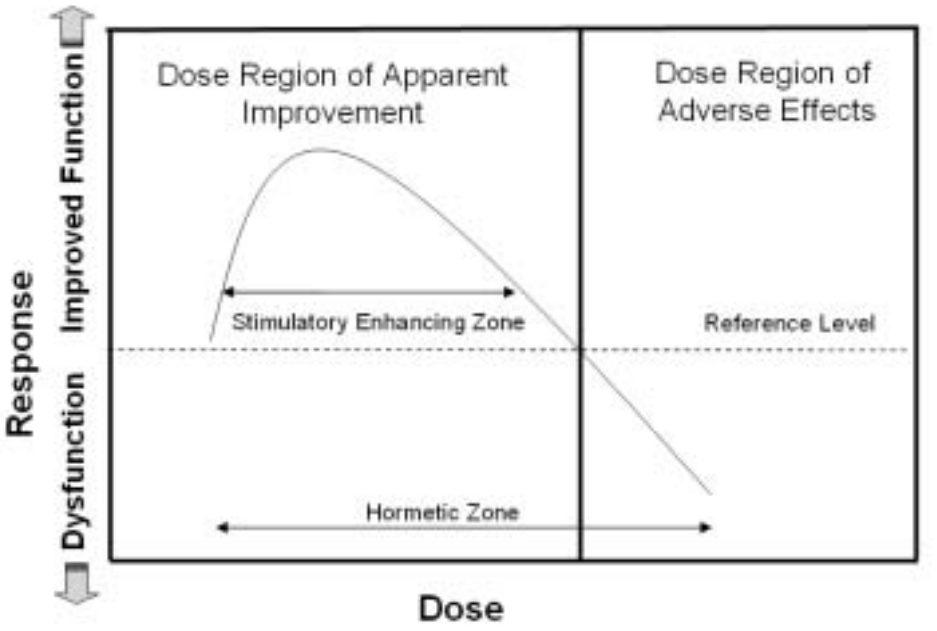

FIGURE 1 Schematic representation of a hormetic function (Figure adapted from Calabrese and Baldwin, 2003).

of this paper is that the definition of a hormetic function by Calabrese and collaborators (1999) implies the presence of a reference level that is based on a control condition (in most cases, a placebo condition). The shape of the dose-response curve is then calculated by taking into account the percentage of changes in the dependent variable, as a function of the control condition or reference level. Consequently, the entire zone above the reference level refers to the stimulatory enhancing zone (the region of apparent improvement), while the zone below the reference level refers to the region of adverse effects. The hormetic zone thus comprises both the stimulatory enhancing zone and the region of adverse effects. Calabrese and Baldwin (2003) reported that in most studies assessed, the amplitude of the hormetic response almost never exceed a factor of twofold greater than the control, and is usually no greater than 130%–160% of the control, regardless of the width of the stimulatory dose range (Calabrese *et al.*, 1999). Moreover, the width of the stimulatory dose range is below a 20-fold increase from placebo in 70% of the cases, and between 20 and 1000-fold increase from placebo in about 25% of the cases.

Among the studies reviewed by Calabrese and collaborators in which hormesis was observed, were those conducted by Yerkes and Dodson (1908) which showed that learning performance in rodents was optimized

by modest amounts of stress but diminished with either too little or excessive stress, i.e. The Yerkes-Dodson law. Here, it is important to note that at that time, Yerkes and Dodson showed that quantitative features of the dose-response could be altered (i.e. the width of the stimulatory enhancing zone), by changing the complexity of the task. This finding is of considerable interest for the field of stress research since it implies that some biological or psychological factors could modify the quantitative dimension of the dose-response curve. The main goal of this review is to describe the hormetic effects of glucocorticoids on cognitive function and to propose some factors that have to be taken into account when assessing the presence of an inverted-U shape function between circulating levels of glucocorticoids and human cognitive performance.

THE NEUROENDOCRINE RESPONSE TO STRESS

One of the most important neuroendocrine systems responding to stress in both animals and humans is the hypothalamic-pituitary-adrenal (HPA) axis (for an overview, see Francis and Meaney, 1999). It is activated when the allostasis of the organism is challenged, situations that are commonly referred to as stress. During a perceived physical or psychological threat, a cascade of hormones is released. First, corticotropin releasing factor (CRF) is released from the hypothalamus, which triggers the subsequent release of adrenocorticotrophin hormone (ACTH) from the pituitary into the bloodstream. Finally, ACTH stimulates the release of glucocorticoids (GCs; cortisol in humans, corticosterone in rats) from the adrenal cortex.

Glucocorticoids have a variety of different effects in target systems throughout the organism, which can be summarized as aiming to increase the availability of energy substrates in different parts of the body, and allow for optimal adaptation to changing demands of the environment. While the activation of the HPA axis can be regarded as a basic adaptive mechanism in response to change, prolonged activation of this system presents a health risk to the organism: The highly catabolic glucocorticoids antagonize insulin and increase blood pressure, thus increasing the risk for developing diabetes, hypertension, and arterial disease. Also, growth and tissue repair is impaired (Meaney *et al.*, 1996). Furthermore, activation of the HPA axis suppresses immune functions, which in a chronic state, can be considered harmful for the organism, since it is associated with increased risk of infection (Munck and Guyre, 1991; Derijk and Sternberg, 1994). Finally, glucocorticoids released from the adrenal glands travel back to the brain and bind to mineralocorticoid (MR; or Type I) and glucocorticoid (GR; or Type II) receptors which are predominantly localized in the hippocampus and frontal lobes, serving as a negative feedback mechanism on HPA axis activity.

IMPORTANT CHARACTERISTICS OF GLUCOCORTICOIDS

Under basal conditions, glucocorticoid secretion exhibits a 24-h circadian profile in which glucocorticoid concentrations present a morning maximum in humans (the circadian peak), and slowly declining levels in the late afternoon, evening and nocturnal period (the circadian trough), and an abrupt elevation after the first few hours of sleep. Circulating glucocorticoids bind with high affinity to two receptor subtypes; the mineralocorticoid (MR or Type I) and glucocorticoid (GR or Type II) receptors. Although both receptor types have been implicated in mediating corticosteroid feedback effects (see Reul and deKloet, 1985), there are two major differences between MR and GR receptors. First, MRs bind glucocorticoids with an affinity that is about 6 to 10 times higher than that of GRs. This differential affinity results in a striking difference in occupation of the two receptor types under different conditions and time of day. Thus, during the circadian trough (the PM phase in humans and the AM phase in rats), the endogenous hormone occupies more than 90% of MRs, but only 10% of GRs. However, during stress and / or the circadian peak of corticosteroid secretion (the AM phase in humans and the PM phase in rats), MRs are saturated, and there is occupation of approximately 67–74% of GRs (Reul and deKloet, 1985).

The second major difference between these two receptor types is related to their distribution in the brain. The MR is exclusively present in the limbic system, with a preferential distribution in the hippocampus, parahippocampal gyrus, entorhinal, and insular cortices. On the contrary, the GR is present in both subcortical (paraventricular nucleus and other hypothalamic nuclei, the hippocampus and parahippocampal gyrus) and cortical structures, with a preferential distribution in the prefrontal cortex (McEwen *et al.*, 1968, 1986; Meaney and Aitken, 1985; Diorio *et al.*, 1993). As we will see in the following sections, the impact of glucocorticoids on cognitive function can be best understood in terms of the differential effects of MR and GR activation (for a complete review, see deKloet *et al.*,1999) in both the hippocampus and frontal lobes, two brain structures critically involved in cognitive function.

GLUCOCORTICOIDS AND HORMESIS: RODENT STUDIES

Two major types of protocols have been used in rodents studies to assess the presence of an inverted-U shape function between circulating levels of glucocorticoids, and cognitive function. The first approach used dose-response studies involving administration of various doses of synthetic glucocorticoids, and assessment of various types of memory performance. The second approach used a hormone removal-replacement protocol in which cognitive function was first assessed after adrenalectomy (which

abolishes the secretion of endogenous glucocorticoids), and after replacement of glucocorticoids in the same animal. Both of these approaches have revealed the presence of a biphasic function between glucocorticoid levels and cognitive function in rodent (for a complete review, see Lupien & McEwen, 1997).

Dose-Response Studies

Some of the strongest evidence for the presence of an inverted-U shape function between circulating levels of glucocorticoids and cognitive function comes from electrophysiological data assessing glucocorticoid impact on long-term potentiation (LTP; for a complete review of other types of memory processes studied with dose-response protocols in animals, see Lupien & McEwen, 1997). LTP is a long-lasting enhancement in synaptic efficacy that occurs in response to high-frequency electrical stimulation (Teyler & Discenna, 1987; Lynch *et al.*, 1988). Long-term potentiation shares many characteristics in common with memory, the most important being its rapid induction and its long duration.

A number of studies have reported that the induction of LTP in the hippocampus is blocked by the administration of glucocorticoids (Dubrovsky *et al.*, 1987; Filipini *et al.*, 1991). The role of glucocorticoids in hippocampal LTP have further been confirmed by studies showing that the acute administration of glucocorticoids in the dentate gyrus of the hippocampus produces LTP (Filipini *et al.*, 1991; Pavlides *et al.*, 1993). In 1991, Bennett and collaborators reported the existence of a negative correlation between the magnitude of LTP in the CA1 population spike in the hippocampus and the level of circulating glucocorticoids, thus suggesting a dose-dependent relationship between glucocorticoids and their detrimental effects on LTP. One year later, Diamond and collaborators (1992) showed that the relation between glucocorticoids and LTP follows more closely an inverted-U shape relationship than a negative linear relation. They described a positive correlation between corticosterone and primed burst potentiation (PBP; which is a low threshold form of LTP; Bennett *et al.*, 1991) at low levels of glucocorticoids and a negative correlation between corticosterone and PBP at high levels of glucocorticoids. These results provided a strong support for the hypothesis that corticosteroids exert a concentration-dependent biphasic influence on LTP.

Hormone Removal-Replacement Studies

Removal of the adrenal glands has detrimental effects on behavior and many authors have tried to reverse these negative effects by administering glucocorticoids. Using this paradigm, many have reported that pre-training (Micco *et al.*, 1979, 1980; Mitchell & Meaney, 1991), as well as post-training

(Bohus & DeKloet, 1981; Veldhuis *et al.*, 1985; DeKloet *et al.*, 1988; Mitchell & Meaney, 1991) administration of glucocorticoids restores an impaired learned behavior or extinction pattern induced by an adrenalectomy. Veldhuis and collaborators (1982, 1983) have further shown that pre-training administration of glucocorticoids blocks the reduction in the pattern of exploratory behavior observed after an adrenalectomy. Because modulation of cortisol levels gives rise to a concomitant modulation of the learning and memory processes, direct implication of corticosteroids in memory function were postulated.

Involvement of MRs and GRs

The demonstration of an inverted-U shape relationship between corticosteroids and LTP led to the question of whether the involvement of glucocorticoids in memory processes involves opposing or synergistic processes that could be mediated by the two types of adrenal steroid receptors reported to exist in the hippocampus and other brain regions.

To test this hypothesis, Pavlides and collaborators (1994) used MRs and GRs agonists and antagonists, alone or in combination with each others, and measured LTP in the dentate gyrus of the hippocampus. The results showed that the inverted-U shape relationship previously described by Diamond *et al.*, (1992) may be explained by a differential activation of MRs and GRs adrenal steroids receptors in the hippocampus. In their study, the activation of MRs receptors led to an increase in LTP while the activation of GRs receptors led to a decrease in LTP. Both these effects were blocked by the administration of their specific antagonist. Similar inhibitory actions of GRs receptor antagonists on the population spike amplitude of hippocampal slice preparations were also obtained using RU 486 (Rey *et al.*, 1989, 1994; Talmi *et al.*, 1992). Moreover, a second study performed by Pavlides and collaborators (1995) showed that the decrease in LTP observed in the dentate gyrus after activation of GRs receptor could in fact be described as the induction of a long-term depression, showing that corticosteroids can have potent delayed suppressive effects on hippocampal plasticity. These authors have suggested that this long-term depression observed after GRs corticosteroid receptors activation in the hippocampus may provide an explanation for the behavioral deficits seen with elevation of glucocorticoids in animal and humans.

GLUCOCORTICOIDS AND HORMESIS: HUMAN STUDIES

Contrary to the rodent literature, very few studies in humans have performed dose-response studies or hormone removal-replacement studies on glucocorticoids and cognitive function. Indeed, most of the human studies performed to this day have assessed the direct effects of a single dose of syn-

thetic glucocorticoids on human cognitive performance. Some of these studies have reported negative effects of glucocorticoids on human cognitive performance, while others have reported no effects, or positive effects. We will first summarize these studies, and will outline the results of the dose-response studies and hormone removal-replacement studies that have been performed in humans. We will then present some factors that could potentially explain some of the discrepancies in the observed data.

THE NEGATIVE EFFECTS OF ACUTE GLUCOCORTICOID INCREASES ON HUMAN MEMORY

Memory Sustained by the Hippocampus

Given the presence of MRs and GRs in the human hippocampus, it has been suggested that acute increases of glucocorticoids should lead to deficits in memory functions sustained by this brain region. The seminal work of Scoville and Milner (1957) in amnesic patients having undergone bilateral hippocampal ablation demonstrated that this structure plays a critical role in memory formation, particularly in declarative memory function. Declarative memory refers to the conscious or voluntary recollection of learned information (such as remembering what one had for breakfast; Squire, 1982, 1987; Cohen, 1984; Thyompson, 1986), whereas non-declarative memory refers to the facilitation of recollection of previous information without a conscious and deliberate intention to retrieve this information (such as measured in priming; Schacter, 1987). This somewhat specialized role of the hippocampus served as the basis for specific hypotheses regarding the effects of glucocorticoids on human learning and memory.

In 1996, Kirschbaum and collaborators took advantage of the declarative / non-declarative memory dissociation within the hippocampus in order to assess whether glucocorticoids would have a specific impact on declarative memory function in humans. They reported that the administration of a low dose of synthetic glucocorticoids led to a significant decrease in declarative memory performance, while it had no effect on non-declarative memory performance. These results suggested that glucocorticoids interact with hippocampal neurons to induce cognitive deficits in humans.

More recently, DeQuervain and collaborators (2000) tested the impact of an acute increase of glucocorticoids as a function of the nature of memory processing. A medium dose of synthetic glucocorticoids was administered either before the acquisition of a word list, immediately after, or just before the retrieval of the list. The results revealed significant impairments in memory when the drug was administered just before retrieval, thus sug-

gesting specific effects of glucocorticoids on the retrieval of previously learned information.

A specific effect of acute glucocorticoid elevations on retrieval process in humans has recently been replicated by Wolf and collaborators (2001). Young and aged men were given a medium dose of synthetic glucocorticoids after having learned a list of 10 words. A second word list was learned and recalled after drug administration. Results showed that glucocorticoids impaired recall of the word list learned before treatment in both groups but did not influence recall of the list learned after treatment. These results go along with previous data obtained by de Quervain *et al.,* (2000) showing that acute exogenous administrations of glucocorticoids have impairing effects on retrieval process.

The in vivo demonstration of glucocorticoid effects on memory retrieval process was recently performed by the group of de Quervain and collaborators (2003) using positron emission tomography (PET). Young subjects were administered a medium dose of synthetic glucocorticoids 24 hours after learning various declarative memory tasks. Brain activation was measured by PET 1 hour after drug administration. Results showed that glucocorticoids induced a large decrease in regional cerebral blood flow in the right posterior medial temporal lobe coupled with impaired cued recall of word pairs learned 24 hour earlier. These results were the first to provide an *in vivo* demonstration that acutely elevated glucocorticoid levels can impair declarative memory retrieval processes that are related to a disturbance of medial temporal lobe function. A similar impairment of retrieval function was recently reported by Buss and collaborators (in press). These authors administered a small dose of synthetic glucocorticoids to young adults, and measured retrieval of past events in their life (autobiographical memory). Results showed that when compared to placebo, glucocorticoids significantly impaired retrieval of past personal events.

Memory Sustained by the Frontal Lobes

In 2000, Sanchez and collaborators (2000) reported that, in contrast to its well established distribution in the rat brain, GR mRNA is only weakly detected in the dentate gyrus and Cornu Ammonis of the macaque hippocampus. In contrast, GR mRNA is strongly detected in the pituitary, cerebellum, hypothalamic paraventricular nucleus and prefrontal cortices. Additionally, using a specific squirrel monkey antibody Patel and collaborators (2000) found that GR receptors were well expressed in the hippocampus, but were more prominently found in the prefrontal cortex.

The almost exclusive presence of GRs in the primate and human frontal lobes led scientists to study the impact of glucocorticoids on frontal

lobes functions. Studies in nonhuman primates (Goldman-Rakic, 1987, 1995) and humans (Petrides and Milner, 1982; Owen *et al.*, 1990) showed that lesions of the dorsolateral prefrontal cortex (DLPFC) give rise to impairments in working memory. Working memory is the cognitive mechanism that allows us to keep a limited amount of information active for a limited period of time (see Baddeley, 1995). Thus, working memory impairments have been found in several experiments using a variety of delay task procedures. In these tasks, a temporal gap is introduced between a stimulus and a response, which creates the need to maintain the stimulus in temporary memory storage. Data obtained in monkeys showed that cells in the lateral prefrontal cortex become particularly active during delayed response tasks, suggesting that these cells are actively involved in maintaining the information during the delay (Goldman-Rakic *et al.*, 1990, 1995).

Neuropsychological evidence suggests that humans with prefrontal damage are impaired in working memory (Luria, 1966; Fuster, 1980). These patients are also highly susceptible to cognitive interference and they perform poorly on neuropsychological tests that require response inhibition such as the Wisconsin Card Sorting Test (Stuss *et al.*, 1982; Shimamura, 1995). Moreover, recent neuroimaging data summarized and reviewed by Smith *et al.*, (1998; see also Dolan and Fletcher, 1997; Ungerleider *et al.*, 1998) show a significant relationship between working memory processing, and activation observed in the prefrontal cortex (Smith *et al.*, 1998; Ungerleider *et al.*, 1998).

In 1999, we reported data showing impairments in working memory function with a high dose of synthetic glucocorticoids in young male subjects (Lupien *et al.*, 1999). In this study, young subjects were infused for 100min. with one of three doses of synthetic glucocorticoids or placebo and working memory function was tested during the infusion period. The results revealed that performance on the working memory task decreased significantly at the highest dose of hydrocortisone. Curve fit estimations revealed the existence of a significant quadratic function (inverted U-shape curve) between performance on the working memory task and changes in glucocorticoids levels after hydrocortisone infusion. The results of this study suggested that in young individuals, glucocorticoids have negative effects on frontal lobe function.

THE ABSENCE OF EFFECTS OF ACUTE GLUCOCORTICOID INCREASES ON HUMAN MEMORY

Although many studies reported impairing effects of acute increases in glucocorticoids on declarative memory performance, other studies reported no such impairing effects on memory functions sustained by the hippocampus and frontal lobe regions.

Memory Sustained by the Hippocampus

In our dose-response study of the effects of hydrocortisone on working memory function, we also measured declarative memory performance under the various doses administered. We found that compared to the impairing effects of hydrocortisone on working memory performance, there was no effects of the drug on declarative memory performance (Lupien *et al.*, 1999). Similar results were obtained by Hsu and collaborators (2003). In their study, twenty healthy subjects were treated with a high dose of synthetic glucocorticoids or placebo orally, in a double-blind, two-way crossover study. The authors measured evoked-related potentials (ERPs) during a declarative memory task, and during an attentional task (the Stroop test). It was found that glucocorticoids impaired performance on the attentional task, while it did not impair performance on the declarative memory task.

Memory Sustained by the Frontal Lobes

In contrast to the results reported above, a recent study by Monk and Nelson (2002) reported impairing effects of exogenous glucocorticoids on declarative memory function, with no impairments in memory function sustained by the frontal lobes. In this study, Monk and Nelson (2003) measured the effects of a medium dose of synthetic glucocorticoids on a declarative memory task (intentional face recognition task with a short and long delay), a working memory task (n-back task) and an attentional task (choice reaction task), while recording ERPs to each task. Results showed that ERPs and behavioral performance were not affected in the attention and working memory tasks, while performance was impaired in the recognition task with a long delay. The authors interpreted this result as showing that declarative memory is more sensitive than working memory to an acute increase of glucocorticoids. However, it is important to note that in the context of this study, it was also found that with the declarative memory task, hydrocortisone was associated with a greater ERP activation to novel stimuli over the frontal lobe and reduced activation to repeated stimuli in more posterior regions of the scalp. This later result suggests that the declarative memory task did not exclusively involve the hippocampus, but rather recruited additional frontal regions.

THE POSITIVE EFFECTS OF ACUTE GLUCOCORTICOID INCREASES ON HUMAN MEMORY

Although seldom thoroughly discussed in the literature pertaining to the effects of glucocorticoids on human learning and memory, it is interesting to note that some studies reported positive effects of glucocorticoids

on human learning and memory. At this point, significant positive effects of glucocorticoids on human memory have only been reported for memory sustained by the hippocampus.

Memory Sustained by the Hippocampus

The first study ever published on the effects of exogenous administration of glucocorticoids on human learning and memory reported positive effects of glucocorticoids. In 1986, Beckwith and collaborators administered four different doses of synthetic glucocorticoids or placebo to young subjects and showed that the effects of glucocorticoids on human memory performance depended upon the dose administered. They reported that only the highest doses of glucocorticoids enhanced the recall of previously presented lists of words, leading to the suggestion that glucocorticoids could have beneficial effects on learning and memory. However, it has to be noted that in this study, Beckwith and collaborators (1986) mixed glucocorticoids with glucose during drug administration so it is unclear whether the reported beneficial effects of glucocorticoids on declarative memory performance were due to glucocorticoids, glucose, or the interaction between the two compounds.

In 2002, Lupien and collaborators measured the effects of a medium dose of synthetic glucocorticoids on declarative memory performance. Results showed beneficial effects of glucocorticoids on the speed of processing of the memory task, suggesting positive effects of glucocorticoids on declarative memory function. However, it is to be noted that since glucocorticoids did not impair performance (error rate) on the declarative memory task, the obtained results could be interpreted as showing a positive effect of glucocorticoids on attentional process (reaction times).

In a recent study, Buchanan and Lovallo (2001) exposed young participants to pictures varying in emotional arousal after they received a small dose of synthetic glucocorticoids. During acquisition, subjects were not aware that their memory for the pictures would be tested a week later (incidental memory). Results revealed that glucocorticoids elevations during memory encoding enhanced the delayed recall performance of emotionally arousing pictures while it had no impact on the delayed recall of the neutral pictures.

Similarly, Abercrombie and collaborators (2003) tested the effects of exogenous administration of two doses of synthetic glucocorticoids on emotional memory using a dose-response study. Young men were presented with emotionally arousing and neutral stimuli after receiving either placebo, or a small or medium dose of synthetic glucocorticoids. Free recall of the stimuli was performed 1 hour after drug administration and recognition memory of the stimuli was performed two evenings later. Results showed that glucocorticoid elevations decreased the number of errors committed on the

free-recall tasks (increased performance). More importantly, the authors showed that when tested for recognition two evenings later, when cortisol levels were no longer manipulated, recognition performance presented an inverted-U quadratic curve, with recognition memory for both emotionally-arousing and neutral stimuli being facilitated at the smallest dose of glucocorticoids. In contrast to the data obtained by Buchanan and Lovallo (2001), these results showed beneficial effects of synthetic glucocorticoids on both emotionally-arousing and neutral material.

Dose-Response

As summarized above within the context of the various studies which have assessed the acute effects of glucocorticoids on human cognitive function, only two studies have assessed the dose-response relationship between glucocorticoids and human cognitive performance. Using a dose-response study, Lupien *et al.,* (1999) reported the presence of an inverted-U shape function between glucocorticoids and performance on a working memory task, and Abercrombie *et al.,* (2002) reported the presence of an inverted-U shape function between glucocorticoids and performance on a task of emotional memory.

Hormone Removal-Replacement

In 2002, our group performed a hormone removal-replacement study of glucocorticoids in a population of young normal controls (Lupien *et al.*, 2002). In this study, we used a within-subject double-blind experimental protocol in which we first induced a chemical lowering of glucocorticoids levels by administration of metyrapone, a potent inhibitor of glucocorticoids synthesis, and then restored baseline circulating glucocorticoid levels with subsequent infusion synthetic glucocorticoids. Memory performance of participants under each of these conditions was compared to that measured on a placebo day. It was postulated that decrease in glucocorticoid levels should lead to impaired memory function, while a replacement of baseline glucocorticoid levels by infusion of hydrocortisone should restore memory performance to the level observed under the placebo condition. The results confirmed the hypothesis as it was shown that, when compared to placebo, the pharmacological decrease of circulating levels of glucocorticoids induced by metyrapone significantly impaired memory performance. Most importantly, we showed that this impairment was completely reversed after hydrocortisone replacement. These results showed that glucocorticoids can modulate memory function, and most importantly, they showed that the absence of circulating glucocorticoids is as detrimental for human memory function, as is a significant increase of glucocorticoids.

Involvement of MRs and GRs

Similarly to Pavlides *et al.,* (1994), we have suggested that this modulation can happen through a differential activation of MRs and GRs (Lupien

et al., 2002). Indeed, during the metyrapone condition, MR occupancy was low, given the significant decrease of glucocorticoids secretion induced by metyrapone. At this point, impairment in memory was observed. On the contrary, during the hydrocortisone replacement condition, glucocorticoid levels were restored to the levels typical of those measured in the AM phase, i.e. leading to a restoration of baseline cognitive performance.

IS THERE REALLY A HORMETIC FUNCTION RELATING GLUCOCORTICOIDS AND HUMAN COGNITION?

Although a wealth of rodent studies have clearly shown the presence of an inverted-U shape function between circulating levels of glucocorticoids and memory, it is clear from the human literature cited in the previous sections that very few human studies have directly tested the presence of an inverted-U shape function within the same experimental context. However, some negative, absent, or positive effects of glucocorticoids have been reported on human memory function. As we have discussed previously, a test of the inverted-U shape function in humans would necessitate either a dose-response protocol similar to the ones used in rodent studies (see Bennett *et al.*, 1991; Diamond *et al.*, 1992), or a hormone removal-replacement protocol (Micco *et al.*, 1979, 1980; Bohus & DeKloet, 1981; Veldhuis *et al.*, 1982, 1983, 1985; DeKloet *et al.*, 1988; Mitchell & Meaney, 1991; Mitchell & Meaney, 1991). The human experiments that have used these protocols have reported the presence of a biphasic curve between circulating levels of glucocorticoids, and cognitive performance (Lupien *et al.*, 1999, 2002; Abercrombie *et al.*, 2002).

Another way to test the presence of a hormetic function in human studies would be to use a similar approach than the one used by Calabrese and Baldwin (2003). In Calabrese & Baldwin's model of hormesis, one of the most important component of the hormetic function is the presence of a reference level that is based on a control condition. For each study, a percentage change from this control condition (here, placebo condition) is calculated, and the results are plotted to assess whether there exists an inverted-U shape function for the compound under study (for a complete description of the methodology, see Calabrese & Baldwin, 2003).

In order to assess whether there is evidence of a hormetic function between circulating levels of glucocorticoids and cognitive performance in the human literature, we have calculated the percentage of changes in each cognitive function tested for each human study showing negative, absent or positive effects of glucocorticoids on human cognition, based on a reference value (performance on the placebo condition). This gives rise to a percentage of increase or decrease of performance in relation to a control value (Calabrese & Baldwin, 2003). In order to assess whether glucocorti-

coids have a different effect for different types of cognitive processing, we have separated the various cognitive functions tested into three main aearas, i.e., declarative memory, attentional/working memory (including results on reaction times), and emotional memory. For the two human studies that have performed a dose-response protocol (Lupien *et al.*, 1999; Abercrombie *et al.*, 2003), we have calculated the same percentage change as a function of that study reference value. Table 1 presents the percentage of changes in cognitive function as a function of the compound used (synthetic glucocorticoid), dose, time of administration, and type of memory assessed for all the studies cited in the previous section. In this Table, the grey zone represents the results of the studies that have performed a dose-response study, while the white zone represents the results of the studies that have measured the effects of a single dose of synthetic glucocorticoids on cognitive performance.

Several important points emerged from this analysis. First, one can see that the the amplitude of the hormetic response is never greater than 133% (maximum of 33% decrease) of the control, regardless of the width of the stimulatory dose range (Calabrese *et al.*, 1999). This result goes along with the findings of Calabrese & Badwin (2003) showing hormetic response in the range of 130% to 160%. Second, one can see that for studies which have assessed declarative memory function, most of the effects reported as a function of a control value are negative, and performance is decreased from 7.4% (DeQuervain *et al.*, 2003), to 33% (Kirschbaum *et al.*, 1996) using doses of synthetic glucocorticoids ranging from 10 to approximately 38mg (0.5mg/kg; Monk & Nelson, 2002). For the study which has assessed the dose-response function of synthetic glucocorticoids (Lupien *et al.*, 1999) there is the presence of an inverted-U shape function with a low dose of glucocorticoids leading to a 10% increase (non-significant) in declarative memory performance, while a high dose (90mg) lead to a 11% decrease (non-significant) in declarative memory. The third interesting fact to emerge from this Table is that for studies that have measured attentional/working memory processes, doses ranging from 5 to 45mg of synthetic glucocorticoids lead to an increase in attentional/working memory performance from 2% to 13%. In contrast, higher doses (90 and 100mg) of synthetic glucocorticoids lead to impaired performance on reaction times (90mg) or performance (100mg). Finally, one can see that studies which have assessed emotional memory report essentially positive effects of glucocorticoids on recall of emotional information, in the range of 10% and 25% with doses of 20mg and 40mg synthetic glucocorticoids respectively.

Altogether, these results would tend to suggest the presence of a hormetic function between glucocorticoids and cognitive function in humans. However, before concluding that such a function indeed exists, many important points will have to be resolved. We summarize them below.

TABLE 1 Percentage response changes as a function of a control (placebo) condition (reference level) for all human studies which have assessed the acute effects of exogenous administration of synthetic glucocorticoids.

DECLARATIVE MEMORY					
Compound	Dose / mg	Time	Dependent Variable	% change / reference level	Reference
Hydro	Appr. 5	AM	Acquisition / Retrieval	10%	Lupien *et al.*, 1999
Hydro	Appr. 45	AM	Acquisition / Retrieval	0%	Lupien *et al.*, 1999
Hydro	Appr. 90	AM	Acquisition / Retrieval	–11%	Lupien *et al.*, 1999
Hydro	10	PM	Acquisition / Retrieval	–33%*	Kirschbaum 1996
Hydro	10	PM	Retrieval	–15%*	Buss In press
Cortisone	25	PM	Retrieval	–13%*	De Quervain 2003
Cortisone	25	PM	Retrieval	–28%*	De Quervain 2000
Hydro	30	PM	Acquisition / Retrieval	–7.4%*	Monk & Nelson, 2002
Hydro	Appr. 38	AM	Retrieval	–7.9%*	Wolf *et al.*, 2001
ATTENTION / WORKING MEMORY					
Compound	Dose / mg	Time	Dependent Variable	% change / reference level	Reference
Hydro	5	AM	Attention / Working Memory Reaction Times	13%	Lupien 1999
Hydro	45	AM	Attention / Working Memory Reaction Times	2%	Lupien 1999
Hydro	90	AM	Attention / Working Memory Reaction Times	–26%*	Lupien 1999
Hydro	35	PM	Attention / Declarative Memory Reaction Times	11%*	Lupien 2002
Hydro	100	PM	Attention / Working Memory / Errors	–9%*	Hsu 2003
EMOTIONAL MEMORY					
Compound	Dose / mg	Time	Dependent Variable	% change / reference level	Reference
Hydro	20	PM	Emotional Memory; Cued Recall Arousing Stimuli	25%*	Buchanan 2002
Hydro	20	PM	Emotional Memory; Recognition Arousing & Neutral Stimuli	25%*	Abercrombie 2002
Hydro	40	PM	Emotional Memory; Recognition Arousing & Neutral Stimuli	10%	Abercrombie 2002

These data are taken from the mean performance of subjects as given in each original paper. The grey zone represents the results of dose-response studies.* Represents significant results. Note that the non-significant results are only reported for the dose-response studies for the sake of comparison with other doses within a given study. The term '*Appr*' refers to the approximate dose given to an individual of 70kg since the dose administered in these studies were in accordance with the subject's weight. Note that the results of the study performed by Beckwith *et al.*, (1986) are not included in the Table because these authors mixed glucose with the various doses of glucocorticoids administered, so the effects are difficult to interpret in relation to the unique effects of glucocorticoids.

HORMESIS: UNRESOLVED ISSUES

Two other interesting facts emerge from this Table. The first one is that for declarative memory function, 78% of the studies cited reported impairing effects of glucocorticoids, while for attentional/working memory function, 60% of the studies reported positive effects of glucocorticoids. For emotional memory, 100% of studies reported positive effects of glucocorticoids. The second one is that high doses of synthetic glucocorticoids administered in the AM phase (45 and 90 mg; Lupien *et al.*, 1999) have very small and non-significant effects on declarative memory function, while lower doses (10 to 38mg) administered in the PM phase have all significant negative effects. The reverse pattern is observed for tasks that have measured attentional/working memory abilities. High dose of glucocorticoids administered in the AM phase (90mg; Lupien *et al.*, 1999) have more impairing effects on attentional/working memory abilities, than high dose (100mg; Hsu *et al.*,2003) administered in the PM phase.

These two facts are important because they suggest that there may exists different factors unerlying the presence of a hormetic function between glucocorticods and cognitive performance. It will thus be important in future research to assess the impact of these factors on the presence and shape of the hormetic function in order to validate the model. Some of the most important factors to take into account are presented in the next section.

THE EXTENT OF COGNITIVE CHANGES INDUCED BY GLUCORTICOIDS (HORMESIS)

Importance of the Reference Level

The observed difference of the effects of exogenous glucocorticoids administered in the AM and PM phase for declarative and attentional/working memory systems is an interesting observation because remember that one of the most important feature of the hormetic function is comparison to a reference level (here, placebo condition; Calabrese and Baldwin, 2003). However, in the studies of the effects of exogenous glucocorticoids administration on cognitive function, we are dealing with a physiological system that has a diurnal cycle and is changing to novel and stressful stimuli. Consequently, the reference level in studies assessing the effects of synthetic glucocorticoids on human cognition will change in the AM and PM phase and in situations of stress (it is thus not a static reference level). Administering synthetic glucocorticoids in the AM phase means administering glucocorticoids to a system that already has high endogenous levels of glucocorticoids. In contrast, administering synthetic glucocorticoids in the

PM phase means administering glucocorticoids to a system that has low endogenous levels of glucocorticoids.

Affinity of MRs and GRs

Remember that given their differential affinity for glucocorticoids, the MRs will be saturated at smaller concentrations of glucocorticoids than the GRs. In their recent paper, De Kloet and collaborators (1999) have reinterpreted the well-known inverted-U shape function between circulating levels of glucocorticoids and cognitive performance in line with the MR/GR ratio hypothesis. In this view, cognitive function can be enhanced when most of the MRs and only part of the GRs are activated (top of the interted-U shape function; increased MR/GR ratio; see Figure 2). However, when circulating levels of glucocorticoids are significantly decreased or in-

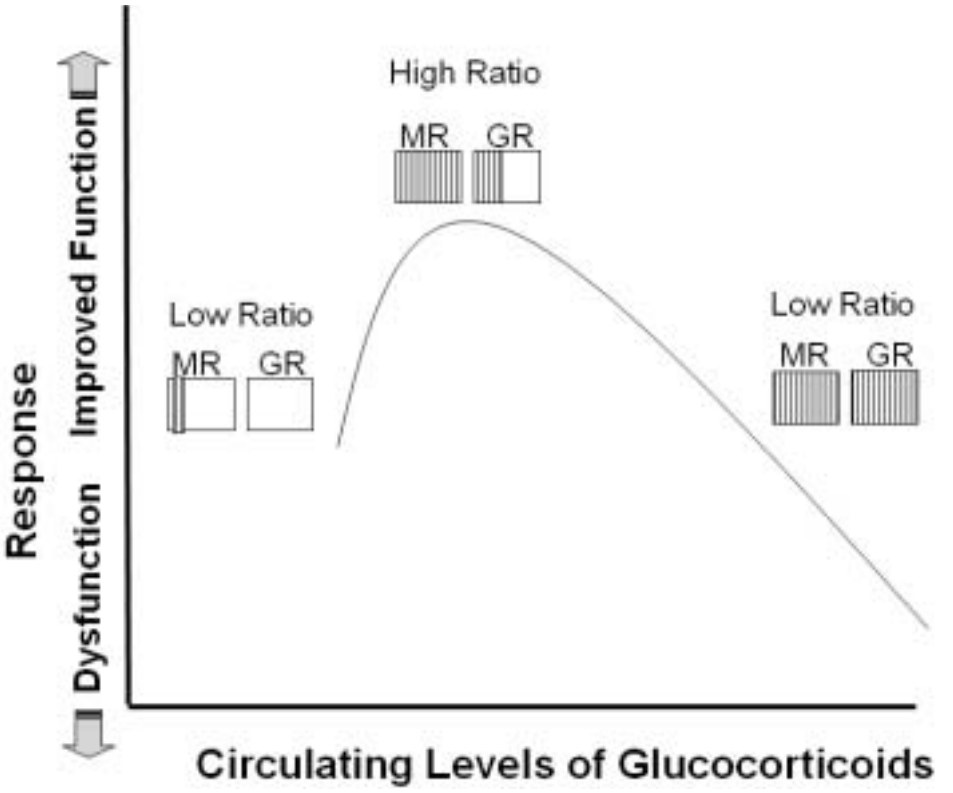

FIGURE 2 Schematic representation of the hormetic function relating circulating levels of glucocorticoids and memory performance. The different ratio of occupancy of MRs and GRs at different circulating levels of glucocorticoids are depicted. The lines within each box represent the relative level of occupancy of each receptor type.

creased (extremes of the inverted-U shape function; low MR/GR ratio), cognitive impairments will result. In rodents, it has been shown that during the circadian trough (the PM phase in humans), the endogenous hormone occupies more than 90% of MRs, but only 10% of GRs. However, during stress and/or the circadian peak of corticosteroid secretion (the AM phase in humans and the PM phase in rats), MRs are saturated, and there is occupation of approximately 67–74% of GRs (Reul and deKloet, 1985).

The proposed model in relation to a MR/GR ratio would suggest that in the AM phase, an optimal level of glucocorticoids is reached, leading to saturation of MRs with almost a full occupancy of GRs (low MR/GR ratio). Administering exogenous glucocorticoids at this time should have little impact on the MR/GR ratio (and consequently memory performance) since the GRs are already occupied at 75%. In contrast, in the PM phase, a suboptimal level of glucocorticoids is observed, leading to high occupancy of MRs (90%) and low occupancy of GRs (10%; high MR/GR ratio). Administering exogenous glucocorticoids at this time should decrease MR/GR ratio (saturate GRs), and consequently, decrease memory performance as compared to placebo. This suggestion would go along with the results of declarative memory function reported in Table 1, although it stands in contrast with a study performed by Fehm-Wolfsdorf and collaborators (1993). These authors reported that under placebo condition, memory performance was higher in the AM phase compared to the PM phase, and they further showed that administration of a medium dose of synthetic glucocorticoids suppressed this circadian variation in memory performance. Moreover, although there is a logical ground for this assumption, it does not explain why administering various doses of glucocorticoids in the AM phase still led to a quadratic function (non-significant) between dose and memory performance (Lupien *et al.*, 1999). The problem that arises from this view is that it is not possible to know how many GRs are occupied with a single dose of glucocorticoids in humans and it is impossible to assess where exactly an individual stands on the inverted-U shape curve before starting an experiment. Consequently, the best way to test this hypothesis would be to perform a dose-response study in the AM and PM phase in humans, and assess the resulting memory performance.

THE NATURE OF COGNITIVE CHANGES INDUCED BY GLUCOCORTICOIDS

Distribution of MRs and GRs

The second fact that emerges from Table 1 is that in contrast to the results observed with declarative memory function, 60% of the studies reported positive effects of glucocorticoids on attentional/working memory abilities. Interestingly, for those studies reporting impairing effects of glu-

cocorticoids on attentional/working memory processes, AM administration lead to more impairing effects than PM administration. This is an interesting finding since remember that MRs and GRs are not distributed evenly in the brain. The MRs are exclusively present in the limbic system, with a preferential distribution in the hippocampus, parahippocampal gyrus, entorhinal, and insular cortices. In contrast, the GRs are present in both subcortical (paraventricular nucleus and other hypothalamic nuclei, the hippocampus and parahippocampal gyrus) and cortical structures, with a preferential distribution in the prefrontal cortex (McEwen *et al.*, 1968, 1986; Meaney and Aitken, 1985; Diorio *et al.*, 1993). This differential distribution of MRs and GRs in the brain suggests that not only the direction (hormesis) of glucocorticoid-induced cognitive changes should vary as a function of MRs and GRs occupancy, but also the nature and/or anatomical substrate of these cognitive changes.

Indeed, based on the MR/GR ratio hypothesis and the distribution of these two types of receptors in the primate (Sanchez *et al.*, 2000; Patel *et al.*, 2000), and human (Sarrieau *et al.*, 1988) brain, one has to come to the conclusion that the anatomical substrate of the cognitive deficits induced by the absence of MR and GR activation should be very different from that induced by a saturation of MRs and GRs. The reason for this lies in the fact that the absence of MR/GR activation would preferentially impact on the hippocampus, while the saturation of MR/GR would recruit additional frontal regions, given the almost exclusive presence of GRs in this region. Although GRs are also present in the hippocampus, many recent reports suggest that the presence of MRs in the hippocampus acts by creating a physiological balance of both types of receptors for their action on the HPA axis [called the "Binary Hormone Response System" by Evans & Arriza (1989) and the "MR/GR balance hypothesis" by Oitzl *et al.*, 1995)]. This suggests that the presence of MRs within a structure acts by decreasing GRs responsivity to glucocorticoids because of the tonic influence of MRs receptors on the HPA axis (Oitzl *et al.*, 1995).

This also implies that the absence of the tonic influence of MRs in the prefrontal regions of the human brain would increase GRs sensitivity to glucocorticoids and lead to increased sensitivity of prefrontal regions to acute increases in glucocorticoid levels, when compared to the hippocampus. This later suggestion could explain why high doses of glucocorticoids administered in the AM phase have more impairing effects on attentional/working memory systems (which are thought to rely on prefrontal regions), compared to declarative memory process (which are thought to rely on hippocampus). Here again, only a dose-response study assessing the effects of various doses of glucocorticoids on attentional/working memory process in humans could explain why a high dose of glucocorticoids administered in the PM phase have so little effect on this type of process.

Differential Effects of MRs and GRs on Memory Process

In 1992, data obtained by Oitzl and de Kloet (1992; recently reviewed by de Kloet *et al.*, 1999), led these authors to suggested that MRs and GRs mediate different effects of glucocorticoids in different time domains. According to this view, MR activation is involved in behavioral reactivity in response to environmental cues (response selection), while GR-mediated effects promote consolidation of acquired information. We have previously argued that what has been called 'response selection' in the rodent literature was similar to the attentional/working memory system described in humans, suggesting that activation of MRs in humans could be involved in the attentional/working memory system while activation of GRs would be involved in the consolidation process (Lupien & McEwen, 1997). Although this view is difficult to reconcile with data showing that the prefrontal regions (which are thought to be involved in working memory function in humans) contains mostly GRs , it is important to note that the hippocampus, which contains a high density of both MRs and GRs has also been shown to be involved in some types of spatial working memory (Wan *et al.*, 1994; Seamans *et al.*, 1998; Lee & Kesner, 2003). Moreover, data obtained by Diamond and collaborators (1999) show that both stress exposure and administration of glucocorticoids impairs performance on hippocampus-dependent working memory tasks, and new data by Roozendaal and collaborators (2004) report that glucocorticoids also impair working memory. It is thus possible that the results observed in human studies for declarative and attentional/working memory process tap on a type of cognitive processing that is sustained partially or totally by the hippocampus. One of the best way to assess the validity of this suggestion would be to administer various doses of glucocorticoids to human subjects, while measuring the pattern of hippocampal and frontal activation by functional brain imaging (pharmacological fMRI).

One Mechanism Underlying the Hormetic Function?

In their 2003 paper, Calabrese and Baldwin reported that one of the most important criticism against the existence of a hormetic function was the fact that no underlying mechanism(s) had been proposed to explain the presence of hormesis (Klaassen, 2000). To this end, Calabrese and collaborators obtained evidence from the pharmacological literature to account for many hormetic biphasic curves that they had reported in the past. They found evidence suggesting that the hormetic function was related to receptor activation, for nearly 30 different receptor systems (see Calabrese and Baldwin, 2003). In most of the studies reported, investigators used synthetic agonists and antagonists to dissect and then reconstruct the biphasic

dose response. This is the approach we have taken in the previous sections, trying to assess the extent and nature of the hormetic influence of glucocorticoids on human cognitive function. If this approach is adequate in explaining the effects of glucocorticoids on human cognitive function, then this implies that differences in the number of MRs and GRs amongst individuals should lead to different memory performance.

Impact of Down-Regulation of Glucocorticoid Receptors on the Hormetic Zone

Results from animal and human studies provide evidence that repeated stress over time is linked to a down-regulation of MRs and/or GRs, leading to a hyperactivity of the HPA axis. In animal studies, chronic ethanol-stress or cold-stress has been linked to a persistent increase in the activity of the HPA axis, which was accompanied by signs of hypertrophy of the adrenal cortex (Spencer and McEwen, 1990; Bhatnagar and Meaney, 1995). Other animal studies have found that the sensitivity of the HPA axis to react to a stressor is enhanced after a period of chronic stress (Checkley, 1996), a finding that has been discussed as sign of increased catecholaminergic input to CRF containing cells after chronic stress (Dallman *et al.*, 1991; Dallman, 1993). In human studies, our laboratory (Pruessner *et al.*, 1999); (Schulz *et al.*, 1997; Wust *et al.*, 2000) and others (Spencer and McEwen, 1990; Melamed *et al.*, 1999; Steptoe *et al.*, 2000) have provided evidence that chronic stress is accompanied by elevated levels of glucocorticoids. Most often, glucocorticoid levels after awakening or in the early morning hours were found to be elevated, although one study reported elevated morning combined with lower evening levels in chronically stressed subjects (Ockenfels *et al.*, 1995).

It has been demonstrated that chronic stress as well as artificial elevations of glucocorticoid concentrations are associated with reduced GR density in the hippocampus, and therefore a loss of glucocorticoid feedback-mediating cells which leads to the hyperactive HPA axis observed after chronic exposure to stress (Henry *et al.*, 1994; Barbazanges *et al.*, 1996; Levitt *et al.*, 1996; Welberg *et al.*, 2000). The expression of MRs seems to be reduced by chronic stress effects as well, although it appears as if the impact of chronic stress on GR expression is more pronounced (Henry *et al.*, 1994).

Based on the MR/GR ratio model (de Kloet *et al.*, 1999), it could be suggested that the inverted-U shape curve relating glucocorticoid levels and memory performance may vary between individuals as a function of the number of MRs and GRs, which in turn, could be determined in each individual by different exposure to acute and chronic stress. If the entire hormetic zone of the inverted-U shape function varies between individuals, then this further suggests that the same dose of glucocorticoids should lead to different memory performance in different individuals.

The rationale behind this hypothesis is the following: Chronic stress has been shown to lead to a significant decrease in GRs, although it is not clear that it also leads to a similar down-regulation of MRs. This means that if someone, due to chronic stress, has a lower number of GRs, this should lead to saturation of GRs at lower circulating glucocorticoid concentrations, which should then contribute to modify the width of the stimulatory dose range of the hormetic function relating glucocorticoids and memory performance. This means that relative to an individual with higher GR expression, an individual with a lower number of hippocampal GRs, fewer circulating glucocorticoids would be required to negatively impact memory function.

These ideas are summarized in Figure 3. In this Figure, Group #1 displays normal levels of GRs, while Group #2 displays a down-regulation of these receptors. Consequently, the inverted-U shape function relating cir-

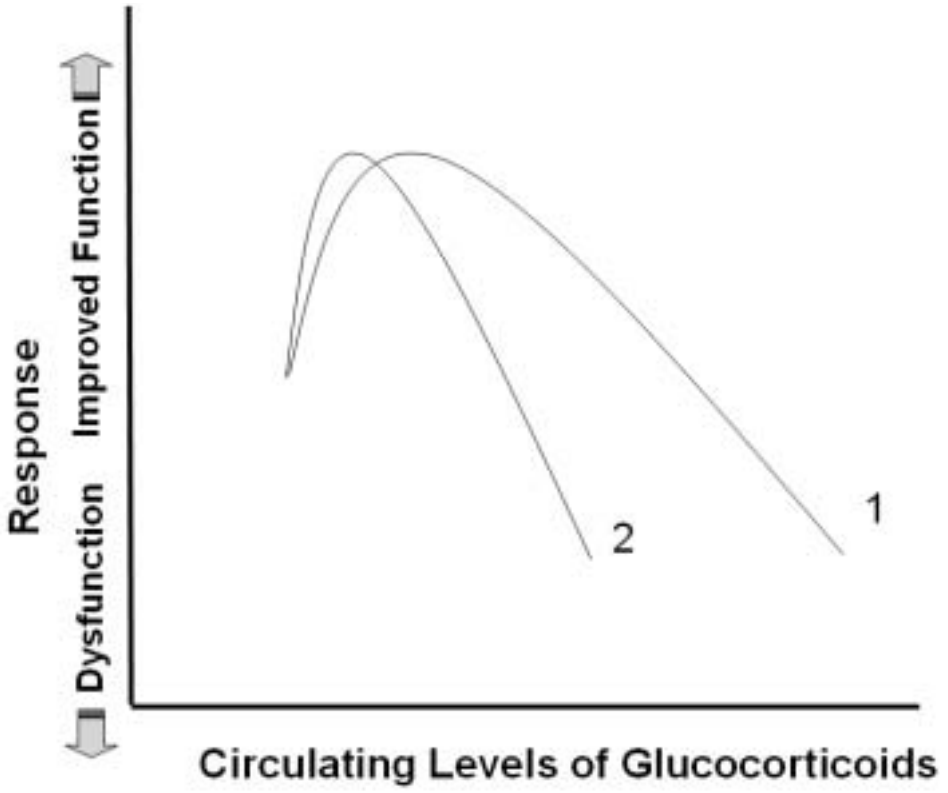

FIGURE 3 Schematic representation of the theoretical change in the shape of the inverted-U shape function glucocorticoids, and memory performance with down-regulation of GRs. Group #1 represents individuals with normal levels of GRs, while Group #2 represents individuals with a down-regulation of GRs.

culating levels of glucocorticoids and cognitive performance in this group will be skewed to the left as compared to the the inverted-U shape function observed in individuals with normal levels of GRs. The net effect of this change will be a smaller width of the stimulatory dose range in the group with low levels of GRs, and thus, impaired cognitive performance at lower levels of glucocorticoids.

Although the above hypothesis is still highly speculative at this point in time, the recent recurrence of the hormesis hypothesis calls for more and more studies assessing the effects of different levels of MRs and/or GRs on the hermetic zone. At this point in time, it is quite difficult to assess the existence of down-regulation of either MRs and GRs in humans, although various neuroendocrine challenge studies provide solid evidence of down-regulation of these receptor types in humans (Otte *et al.*, 2003). Moreover, other studies report the presence of down-regulation of hippocampal GRs during opiate withdrawal in rodents (McNally and Akil, 2003), during amygdala kindling (Kalynchuk & Meaney, 2003), in schizophrenia and mood disorders in humans (Webster *et al.*, 2002), and after chronic exposure to stress (Henry *et al.*, 1994; Barbazanges *et al.*, 1996; Levitt *et al.*, 1996; Welberg *et al.*, 2000). The presence of a down-regulation of MRs and/or GRs in a specific population could thus permit to test the MR/GR ratio model in humans, using the types of predictions suggested in this paper.

MANY MECHANISMS UNDERLYING THE HORMETIC FUNCTION? :

In the same 2003 paper, Calabrese and Baldwin also reported that evidence accounting for the hormetic function could be at levels of further complexity, which led the authors to state that *'there is no single hormetic mechanism. Each endpoint considered in an hormetic evaluation may be affected by a different receptor system (or by interacting receptor systems). What each mechanism does have in common is the quantitative feature of the dose-response curve'* (Calabrese & Baldwin, 2003).

We believe that such a complex mechanism underlies the hormetic influence of glucocorticoids. There are two main reasons for this belief. The first lies in the fact that in contrast to declarative and attentional/working memory performance, 100% of studies assessing the effects of glucocorticoids on emotional memory reported positive effects. This suggests that the mechanisms underlying the effects of emotional information on human memory function are influenced by glucocorticoids. The second lies in the fact that during exposure to a stress or an emotion, there is the release of both glucocorticoids and catecholamines, as well as many other hormones and neurotransmitters. Although very few studies have assessed the combined influence of glucocorticoids and catecholamines on cognitive function in humans, many rodent studies have shown that many of the effects of glucocorticoids on memory are related to noradrenergic activation of

the basolateral complex of the amygdala (for a complete review, see Roozendaal, 2002). Altogether, these results imply that the direction of the effects of glucocorticoids on cognitive performance could depend on the interaction of glucocorticoids with other hormonal or neurotransmitter systems. Furthermore, the nature of these interactions could be greatly influenced by the context associated with the stressful experience. The last section of this paper summarizes the results of studies going along with this suggestion.

Stress versus Arousal Influences on Memory

In a paper published in 2003, Woodson and collaborators raised an important point about the influence of glucocorticoids on memory performance. They stated that while elevated glucocorticoid levels are generally viewed as a physiological marker of a stress state, there are many other conditions (e.g. feeding, sex, and exercise; Moberg *et al.*, 1975; Phoenix *et al.*, 1977; Bronson & Desjardins, 1982; Rosmond *et al.*, 2000; Kanaley *et al.*, 2001; Makatsori *et al.*, 2003) that induce significant elevations of glucocorticoids, without necessary impairing cognition. The question then arised as to whether the cognitive changes induced by glucocorticoids are due to the arousal feature of the situation, or to the stressful nature of the situation. In order to test this, they performed the following experiment. In a first study, they compared the effects of predator exposure on a hippocampus-dependent spatial working memory task, to that of a retrieval or spatial reference memory, that does not tap on hippocampal process. They reported that cat exposure selectively impaired working (hippocampus-dependent), but not reference (hippocampus-independent) memory. In a second experiment, they assessed whether spatial working memory was impaired because of the fear-provoking (stressful) nature of predator exposure, or because the cat (predator) was a novel and arousing stimulus. They compare the effects of an appetitive stimulus (exposure to a sexually receptive female) versus an aversive stimulus (cat exposure) on spatial working memory performance. They found that although glucocorticoid levels were increased at a comparable level in the cat- and female-exposed groups, only the cat-exposed group committed a significant increase in the number of errors in the spatial working memory task. It was also found that only the cat-exposed rats exhibited a significant correlation between glucocorticoid levels and impaired memory. Altogether, these results showed that hippocampus-dependent memory tasks are sensitive to cat exposure and that it is the fear provoking nature of the stimulus, rather than the arousing nature of it, that impaired spatial working memory.

Similar results were recently obtained by Okuda and collaborators (2004) who reported that the effects of glucocorticoids on object recognition memory depend on novelty of the training situation. The authors stud-

ied the effects of post-training injection of various doses of glucocorticoids on 24h delayed memory in rats that were previously habituated to the experimental context and in rats that were exposed to the experimental context for the first time. The results showed that only in rats that were not previously habituated to the experimental context did glucocorticoids enhanced 24h retention performance in an inverted-U shape dose-response relationship. Altogether, these results suggest that the effects of glucocorticoids on memory performance depend on the nature of the situation that induced a release of glucocorticoids in the first place.

The Importance of Context

These results are important because they raise the notion of context when assessing the effects of glucocorticoids on cognitive performance. Many studies have shown that increased glucocorticoid levels contribute to the enhancement of memories central to the stressful experience (remembering the elements that induced the stress), while the same increased glucocorticoid levels impair memory of events that occurred outside of the context (Sandi, 1998; de Kloet *et al.*, 1999; Diamond *et al.*, 2001; Cordero *et al.*, 2002; Roozendaal, 2002; Roozendaal, *et al.*, 2003; Akirav *et al.*, 2004). However, in humans, a recent study by Cahill and collaborators (2003) reported that when the out-of-context information to be remembered after stress is emotional, glucocorticoid can also potentiate recall of this emotional information. These authors presented emotionally arousing or neutral slides to their subjects and, after viewing the slides, participants were submitted to the cold pressor stress (CPS; immersion of forearm in ice-cold (0°–3°C) water) or to a control situation (immersion of forearm in warm (37°–40°C) water). Results showed that, in contrast to the control situation, CPS significantly elevated salivary cortisol levels. Furthermore, CPS, as compared to the control situation, enhanced post-stress long-term (1 week delayed recall) declarative memory for emotionally arousing slides, without influencing memory for the neutral slides. These results suggest that, in humans, high stress-induced increases in corticosteroids may enhance memory for previously learned material that is emotionally arousing in nature, even if this material is not related to the stressor.

This dissociation of the effects of glucocorticoids on memory (neutral *versus* emotional) could explain why 100% of the studies reported in Table 1 and assessing emotional memory have reported enhancing effects of glucocorticoids on memory for emotional events, while 78% of the studies assessing declarative memory have reported impairing effects of glucocorticoids. In the former type of studies, subjects were asked to recall information central to the emotional experience, while in the later, subjects were asked to recall information outside the context of the experience.

These data are to be placed in relation with a new model proposed by Roozendaal (2002) which suggests that the effects of glucocorticoids on cognition not only depend on the type of information to be remembered, but also depend on the different phase of memory investigated. Here it is important to note that although many studies have measured the effects of glucocorticoids on subsequent learning of a new information, in most cases, human subjects were tested shortly after training, while glucocorticoid levels were still elevated. These protocols prevent one from assessing the differential effects of glucocorticoids on acquisition versus retrieval, and led to the hypothesis that glucocorticoids can directly affect retrieval performance.

The model of Roozendaal (2002) suggests that glucocorticoid enhance memory consolidation while they impair memory retrieval such that once memories are consolidated, the efficacy (or accuracy) of the information retrieved would remain vulnerable to the effects of glucocorticoids at the time of recall. These results would go along with most data presented in Table 1 for declarative memory, where the totality of the studies have assessed glucocorticoid effects on encoding and retrieval, and with the studies performed by deQuervain *et al.,* (2000, 2003), Wolf *et al.,* (2001), and Buss (in press) who have specifically shown the detrimental effects of glucocorticoids on retrieval process. This glucocorticoid-induced memory retrieval impairment would depend, in part, on activation of GRs in the hippocampus (Roozendaal, 2002), a view that may seem different from the one proposed by DeKloet *et al.,* (1999) who suggests a role of GRs in the process of consolidation.

Is There More Than One Player?

However, recent data suggest that the dissociation of effects of glucocorticoids on consolidation and retrieval could be related to the fact that during consolidation, glucocorticoids interact with the noradrenergic system in order to modulate memory function (for a complete review, see Roozendaal, 2002). The model of Roozendaal and McGaugh (1996a, 1996b, 1997a, 1997b; Roozendaal *et al.,* 2002, 2003) suggests that glucocorticoids influence memory through interaction with noradrenergic receptors in the amygdala. The amygdala expresses a moderate density of GRs (Honkaniemi *et al.,* 1992; Morimoto *et al.,* 1996) and there are extensive observations indicating a critical role of the amygdala and the noradrenergic system in mediating the effects of stress hormones on memory (see McGaugh, 2000; Roozendaal, 2002). For example, systemic administration of a beta-adrenoceptor antagonist, or direct infusion of a beta-adrenoceptor antagonist into the basolateral complex of the amygdala block the glucocorticoid-induced increase of memory consolidation (Quirarte *et al.,* 1997; Roozendaal *et al.,*

2002). However, the modulatory effects of glucocorticoids on cognitive function may not depend solely on the basolateral nucleus of the amygdala, since glucocorticoid infusions into the basolateral nucleus are insufficient to impair memory retrieval (see Roozendaal, 2002 for a review).

In a recent human study, we tested the influence of the noradrenergic and glucocorticoid system on memory for neutral versus emotional information. Young men were administered a placebo, a β-adrenergic receptor blocker (propranolol), or an inhibitor of glucocorticoid secretion (metyrapone) and short-term (5 minutes) and long-term (1 week) recall of a story composed of neutral and emotional segments was assessed. Results showed that administration of the β-adrenergic receptor blocker impaired both short- and long-term memory for emotionally-arousing material, while administration of an inhibitor of glucocorticoid synthesis did not impair short-term memory, but impaired long-term memory for both emotionally-arousing and neutral material (Maheu *et al.*, 2004). These results demonstrated that adrenergic and corticosteroid hormonal systems differentially impact memory for emotionally-arousing and neutral material, and suggested the presence of an interaction between adrenal hormones for the modulation of emotionally-arousing memory in humans. Future dose-response studies using both types of compounds alone or in combination could provide very valuable data on the unique and shared effects of these two hormonal systems for the modulation of human memory.

CONCLUSION

Today, the Yerkes-Dodson (1908) law is only part of a growing body of evidence showing the presence of an inverted-U shape function between biological and cognitive functions. The inverted-U shape effects of glucocorticoids on cognitive function are robust, suggesting that some particular mechanism may explain the presence of a hormetic function for glucocorticoids and cognitive function in humans.

In this paper, we first summarized the negative, absent, and positive effects of acute increases of glucocorticoids on human learning and memory, and we discussed some factors that have to be taken into account in order to confirm the presence of a hormetic function for glucocorticoids and human cognitive performance. This led us to suggest that the hormetic function relating glucocorticoids and cognition could be explained by a dynamic interplay between glucocorticoids and the noradrenergic system (with a particular emphasis on the amygdala) for modulation of memory function, and down the line, by interactions of these two systems with other brain regions. If this is the case, then it is quite possible that the hormetic influence of glucocorticoids on human cognitive function is the empiric representation of the interplay between various systems of the brain trying to act on and/or counteract the effects of stress on cognitive performance.

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